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PERSPECTIVES

The Case for Intervention Bias in the Practice of Medicine

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Bias is an inclination to present or hold a partial perspective at the expense of possibly equal or more valid alternatives. In this paper, we present a series of conditional arguments to prove that intervention bias exists in the practice of medicine. We then explore its potential causes, consequences, and criticisms. We use the term to describe the bias on the part of physicians and the medical community to intervene, whether it is with drugs, diagnostic tests, non-invasive procedures, or surgeries, when not intervening would be a reasonable alternative. The recognition of intervention bias in medicine is critically important given today's emphasis on providing high-value care and reducing unnecessary and potentially harmful interventions.

INTRODUCTION

Bias is an inclination to present or hold a partial perspective at the expense of possibly equal or more valid alternatives. In this paper, we argue that *intervention bias*,

which has not been previously described, exists in the practice of medicine. We use the term to describe the bias on the part of physicians and the medical community to intervene, whether it is with drugs, diagnostic tests, non-invasive procedures, or

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†Abbreviations: CAD, coronary artery disease; AF, atrial fibrillation; VT, ventricular tachycardia; ACCORD, Action to Control Cardiovascular Risks in Diabetes Trial; ACC, American College of Cardiology; ACS, American College of Surgery; ACOG, American College of Obstetrics and Gynecology; OECD, Organization for Economic Cooperation and Development; HTN, hypertension; NHANES, National Health and Nutrition Examination Survey; MI, myocardial infarction; CKD, chronic kidney disease; CAST, Cardiac Antiarrhythmic Suppression Trial.

Keywords: evidence-based medicine, contradicted findings, medical reversal, bias, overtreatment, positive-outcome bias, observational studies, basic science, randomized controlled trials

surgeries, when *not* intervening would be a reasonable alternative. We will present a series of conditional arguments to support the existence of intervention bias in medicine. We will then explore possibilities for why intervention bias exists. Next, we will discuss its consequences. We will conclude the paper by addressing criticisms of intervention bias.

CONDITIONAL ARGUMENTS

The first conditional argument is: *If* intervention bias exists in medicine, *then* physicians, when presented with the option to intervene or not, more often choose intervention when not intervening would be a reasonable choice. Klingman et al. collaborated with leaders of three medical societies, the American College of Cardiology (ACC†), the American College of Surgery (ACS), and the American Congress of Obstetrics and Gynecology (ACOG), to design and conduct surveys of their members using hypothetical clinical scenarios to find out how they would act in each case and why [1]. Their goal was to evaluate how often physicians performed unnecessary tests and procedures for defensive reasons. They found that defensive medicine did exist in their cohort, although not to the extent they expected. Only 8 percent of interventions were undertaken primarily due to malpractice concerns. However, in all of the scenarios, the majority of physicians chose aggressive patient management styles even though conservative management was considered medically acceptable. In most of these cases, perceived medical indications, not malpractice concerns, motivated clinical choices. For example, nearly 60 percent of cardiologists would get either an exercise EKG or stress thallium study on a healthy, active 42-year-old man with no risk factors for coronary artery disease (CAD) who presented to the ER with non-cardiac chest pain (i.e., pain with rotation of the left shoulder), a normal EKG, and negative cardiac enzymes [1]. In another case, almost two-thirds of cardiologists would hospitalize a 50-year-old woman who fainted in a hot

church but had no history of other serious problems and was found to be orthostatic on physical exam [1]. Eighty-three percent would get a holter monitor, 83 percent an echocardiogram, 40 percent a tilt table test, and 40 percent a stress test [1]. In another vignette-based study, Ayanian and Berwick found that pediatricians displayed a propensity toward action when faced with decisions to recommend tympanostomy tube placement or to order radiography in the ambulatory setting [2]. Their methods and results closely mirrored those of a classic study conducted by the American Child Health Association in 1934, which found that school physicians were biased toward intervention when it came to recommending tonsillectomy [3]. This evidence shows that physicians, when presented with the option to intervene or not, more often choose intervention when not intervening would be a reasonable choice. Therefore, intervention bias exists.

The second conditional argument is: *If* intervention bias exists in medicine, *then* physicians will adopt futile and potentially harmful interventions based on scientific theory alone, observational data, inappropriately designed trials and/or those using only surrogate endpoints. Notorious cases include treatment of anemia in patients with chronic kidney disease (CKD) [4], vertebroplasty [5,6], anti-arrhythmic medications to suppress ventricular ectopy post myocardial infarction (MI) [6], routine stenting for stable coronary disease [7-11], rhythm control for atrial fibrillation (AF) [12], screening mammography [13] and PSA testing [14], preoperative MRI for the management of breast cancer [15,16], and goal-directed blood pressure and diabetic management [17-20]. For example, in CKD, strong epidemiologic evidence links anemia to a host of adverse outcomes, including cardiovascular events and mortality [21-23]. This led to the widespread use of erythropoiesis stimulating agents to treat anemia with little more evidence than their ability to raise the hemoglobin and reduce the need for transfusions. However, subsequent randomized controlled trials have shown that this very

expensive therapy may indeed be harmful compared to placebo and certainly so if attempts are made to raise the hemoglobin to near normal [4,24-26]. A similar case applies to ventricular ectopy, which was found to be a strong, independent predictor of total and sudden cardiac death in the first 6 months following acute MI [27]. This led to the widespread use of anti-arrhythmic drugs to suppress ventricular ectopy in post-MI patients without any evidence suggesting they improved hard endpoints. Finally, the Cardiac Antiarrhythmic Suppression Trial (CAST) showed that these drugs conferred greater mortality than placebo, and the practice was subsequently curtailed [7]. This evidence shows that physicians often adopt futile and potentially harmful interventions without adequate evidence. Therefore, intervention bias exists.

Medical reversal is the term used by Prasad and Cifu to describe the process in which a new clinical trial, superior to its predecessors, contradicts current clinical practice [28]. It does not mean that for every indication and purpose the therapy in question was shown not to work, but simply that it was contradicted for key indications. Prasad et al. examined a large collection of high-impact literature and found that among articles making a claim regarding a medical practice, 13 percent were medical reversals [29]. Ionidis has shown that 16 percent of highly cited articles were contradicted by future studies [30]. One could argue that medical reversal does not prove the existence of intervention bias and that using it to do so is an unfair, post hoc indictment of the physician who, in good faith but without full knowledge, has striven to attend to his patients. This ignores the fact that the first rule of medicine is not “to do good” but emphatically “to do no harm.” When viewed from this perspective, jumping on the bandwagon of new interventions “in good faith but without full knowledge” is proof that intervention bias exists. DiNubile argues that “in our modern era of unprecedented scientific growth,” contemporary physicians have become more willing to accept the “latest and greatest” without careful scrutiny and that as

a profession, physicians “seem more preoccupied with sins of omission and less concerned about errors of commission” [31].

The third conditional argument is: *If* intervention bias exists in medicine, *then* interventions will persist on an individual and systemic level after their benefit has been seriously challenged or disproven. Kadivar et al. conducted a vignette-based survey and found that a high percentage of physicians report offering non-evidence-based breast (76.5 percent) and colorectal (39.3 percent) cancer screening tests for young women [32]. In another vignette-based survey of physicians offering women’s primary care, Baldwin et al. found that 28 percent believed that ovarian cancer screening was effective, despite evidence to the contrary, and that a substantial portion reported routinely offering or ordering it [33]. Yabroff et al. conducted a cross-sectional survey of primary care physicians and found that their recommendations for PAP test screening are not evidence based and reflect an overuse of screening [34]. Trottier and Taylor conducted a survey of critical care physicians at a time when PAC use was being questioned based on the results of new data suggesting it was not helpful and could be harmful. They found that 76 percent favored a prospective, randomized, controlled trial involving PAC, but at the same time, 95 percent felt that a moratorium on further use was not warranted [35]. The most important examples of medical reversal being disregarded are recommendations for goal-directed blood pressure and diabetic management. In these instances, data from randomized trials indicate that while treatment may be better than no treatment in certain cases, targeting a specific level is not more beneficial and may in fact be harmful [17-20]. However, based on recommendations from professional guidelines, treatment to these targets is required to meet quality of care standards [36,37]. This evidence shows that interventions persist on both an individual and systemic level after their benefits have been seriously challenged or disproven. Therefore, intervention bias exists.

The fourth conditional argument is: *If* intervention bias exists in medicine, *then*

physicians and medical scientists acting as investigators, manuscript reviewers, and journal editors will be more likely to submit or accept manuscripts for publication that have positive findings related to intervention and to ignore or reject negative studies — this is formally known as *publication bias* or *positive-outcome bias*. In one landmark study, Emerson et al. randomly assigned 210 reviewers for orthopedic journals to receive either a positive or negative test manuscript. The manuscripts were identical in the “Introduction” and “Methods” sections but varied in the “Results.” In one test manuscript, postoperative antibiotics compared to no antibiotics reduced the risk of a surgical-site infection, and in the other manuscript, they did not. Reviewers were significantly more likely to recommend the test manuscript that favored postoperative antibiotics [38]. The reviewers also identified significantly more errors in the manuscript with no difference [38]. Turner et al. evaluated 74 FDA-registered studies of 12 antidepressant agents involving 12,564 patients [39]. A total of 37 studies viewed by the FDA as having positive results (favoring the agent compared to placebo) were published; one study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results (not favoring the agent compared to placebo) were, with three exceptions, either not published (22 studies) or published in a way that, in the authors’ opinion, conveyed a positive outcome (11 studies). This evidence shows that positive findings related to intervention are more likely to be submitted and accepted for publication. Therefore, publication bias exists and, hence, so too does intervention bias.

It is possible that publication bias contributes to intervention bias by giving physicians the imprimatur of printed support for a therapy. If this is true, then one could argue that publication bias is not proof of intervention bias but rather a cause of it. But this begs the question, why is there publication bias? It would seem logical that it exists because of physicians’ and the scientific communities’ bias toward intervention. After all, what makes a study positive is its rejection

of the null hypothesis in favor of an intervention or in favor of a finding that represents a target for intervention. Therefore, it makes the most sense that intervention bias causes publication bias, which, in turn, facilitates more intervention.

CAUSES

Why does intervention bias exist in medicine? It is likely the manifestation of two well-recognized forms of bias, *self-interest bias* and *confirmation bias*. Theories of political and economic science view self-interest as the ultimate goal of many aspects of human behavior. It also appears that self-interest plays a strong role in attitude judgment and persuasion. Through a series of experiments, Darke and Chaiken showed that self-interest biases attitude judgment in a directional manner [40]. Because intervention is often in the self-interest of physicians and the health care industry from a financial perspective, it could bias them to more easily accept arguments in favor of intervention and less inclined to accept those who go against it. Prasad and Cifu cite that “financial incentives are strongly aligned to promote new technologies ... conflicts of interest among trialists, industry-sponsored studies, and industry-sponsored economic analyses all encourage wrongful optimism, facilitating approval” [28]. Neuman et al. found that 52 percent of panel members producing clinical practice guidelines in the United States and Canada on screening, treatment, or both for hyperlipidemia or diabetes had financial conflicts of interest [41]. But financial conflicts of interest are not the only conflicts of interest that can influence recommendations from expert panels. DiNubile was concerned that a lifetime of work invested in a particular disease, test, or discovery will naturally manifest itself as overzealous recommendations from some experts [31]. From this vantage point, problematic guidelines in favor of intervention can be challenged as the exaggerated products of uncensored enthusiasm [20].

The act of intervention could serve physicians’ self-interest in yet another way.

According to Ayanian and Berwick, “clinical satisfaction may be greater for doctors when they recommend an intervention, giving a sense of greater activism in their patients’ care” [2]. For many physicians, the ability to intervene is tied directly to job satisfaction and personal fulfillment. Those who sub-specialize often do so based on their affinity for the nature of the interventions involved. Therefore, their ability to render judgments about the appropriateness of intervention would be affected by self-interest bias.

Confirmation bias is the tendency of people to favor information that confirms their beliefs or hypotheses. It is harmful to objective evaluation, which is required as part of the scientific method. One explanation offered for medical reversal by Prasad and Cifu was “[an] unjustified confidence [hubris] in basic science models and surrogate outcomes” [28]. This could be explained by confirmation bias. Confirmation bias may also explain why individual physicians favor interventions based on anecdotal evidence even after medical reversal. An experimenter’s confirmation bias could affect which data are reported. Data that conflict with the experimenter’s expectations may be more readily discarded as unreliable, producing the so-called “file drawer effect.” The finding by Turner et al. that 60 percent of negative trials registered with the FDA were not reported confirms this [39]. Confirmation bias can also explain why data that conflicts with reviewers’ expectations would more likely be dismissed, as Emerson’s study suggests [38].

Fear of malpractice is also a likely contributor to intervention bias. Alpert refers to defensive medicine and the need for tort reform as the “800-pound gorilla sitting squarely in the middle of the U.S. healthcare system” [42]. He goes on to state that “the current medical liability environment in the United States has resulted in the widespread practice of defensive medicine, which in turn has led to staggering volumes of unnecessary diagnostic testing” [42]. According to Kowey, “defensive medicine is pervasive and takes many forms. It extends

from ordering too many tests all the way to performing unnecessary surgical procedures” [43]. One mail survey of physicians in six high-risk specialties in Pennsylvania found that nearly all (93 percent) reported practicing defensive medicine and “assurance behavior” such as ordering tests and performing diagnostic procedures was very common (92 percent) [44]. A national survey administered by the AMA found that an overwhelming majority of respondents (91 percent) reported believing that physicians order more tests and procedures than needed to protect themselves from malpractice suits [45]. A survey of medical students’ and residents’ experiences with defensive medicine found that 92 percent and 96 percent, respectively, reported encountering at least one assurance practice [46]. These survey results suggest that fear of malpractice may be the overwhelming cause of intervention bias; however, results from Klingman’s landmark study strongly contradict this. As reported under the first conditional argument, Klingman et al., working with three medical societies (ACC, ACS, and ACOG), designed and conducted surveys of their members using hypothetical clinical scenarios to find out how they would act in each case and why [1]. They found that defensive medicine does exist, although not to the extent suggested — only 8 percent of interventions were undertaken for defensive reasons. However, in all of the scenarios, many physicians chose aggressive patient management styles even though conservative management was considered medically acceptable by the expert panels. In most of these cases, perceived medical indications, not malpractice concerns, motivated clinical choices. Also, fear of malpractice would play a minor role, if any, in influencing professional guidelines that have been responsible for codifying overtreatment in certain cases like goal-directed blood pressure and glucose management [33,34].

Moral hazard due to third-party payment for health care services also likely contributes to intervention bias. Traditional health insurance reimburses as a function of expenditure or use. Because insurance

drives the marginal price of medical care at the point of use to near zero, consumers — or physicians acting as their agents — demand care until the marginal product of additional care is nearly zero. Studies have found that a fully insured population spends about 40 percent to 50 percent more than a population with a large deductible, and their status is not measurably improved by the additional services [47]. Oboler et al. found that the majority of patients expect more care than is prudent to deliver [48]. Sixty-six percent of respondents believed that in addition to regular care, an annual physical examination is necessary. Many tests, including Papanicolaou smear (75 percent), mammography (71 percent), cholesterol measurement (65 percent), prostate-specific antigen test (65 percent), urinalysis (40 percent), blood glucose measurement (41 percent), fecal occult blood testing (39 percent), and chest radiography (36 percent), were desired. Interest in these tests decreased substantially when the charges were known.

The problem of moral hazard is likely compounded by the use of patient satisfaction surveys that are being widely used as health care quality metrics. Fenton et al. found that in a national survey of 51,946 adults conducted between 2000 and 2007, higher patient satisfaction was associated with greater inpatient use, higher overall health care and prescription drug expenditures, and increased mortality [49]. Studies have shown that physicians often give in to whatever patients want, whether it is medically necessary or not. Wilson et al. found that patients' perceived need for radiological studies was significantly associated with use of those services for outpatients with respiratory problems and low back pain [50]. In another study, 36 percent of physicians told researchers they would yield to a patient who asks for a clinically unwarranted magnetic resonance imaging exam [51].

Finally, waning clinical skills and lack of confidence in clinical judgment promote a bias toward intervention, especially the overutilization of diagnostic testing. This situation has been lamented by several commentators. Christopher Feddock, on behalf

of the Association of Professors of Medicine, writes that “technology seems to be replacing basic medical skills rather than complementing them” [52]. Herbert Fred describes the period of 1975 to 2003 as the “the laboratory-centered, high-tech years” of medical training [53]. The high-tech diagnostic approach, according to Fred, shifted focus from the patient to the laboratory and gave rise to what he termed “technologic tenesmus — the uncontrollable urge to rely on sophisticated medical gadgetry for diagnosis” [53]. As proof of concept, Penumetsa et al. found that 68 percent of patients who presented to an academic, tertiary care center with chest pain and a very low pretest probability of CAD (< 10 percent) underwent stress testing after ruling out for myocardial infarction [54]. Patients falling into this category would be young with either non-cardiac or atypical chest pain. Based on Bayesian principles for clinical decision making, stress testing is illogical in this patient group.

CONSEQUENCES

What are the consequences of intervention bias? For one, informed decision making relies on the validity of unbiased, balanced, and objective data from published studies, independent of the reported outcome. This is corrupted by intervention bias, rendering clinical recommendations flawed toward specific intervention strategies. Next, intervention bias can lead medical professionals to violate the principle of “*primum non nocere*” or “do no harm.” This can occur whenever interventions are undertaken without rigorous experimentation and that persist after medical reversal. Goal-directed blood pressure management calls for certain high risk groups to achieve a blood pressure level of less than 130/80 mmHg. The most definitive blood pressure targeting trial was the Action to Control Cardiovascular Risks in Diabetes (ACCORD) study [15]. At 4.7 years, there was no difference in the primary end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, despite achieving a significant difference in

mean systolic blood pressure after the first year (119.3 vs 133.5 mmHg). There was a significant increase in serious adverse events in the intensive-therapy group (3.3 percent vs 1.3 percent, $P < .001$). Therefore, in regard to intensive blood pressure management based on results from the ACCORD trial, the number of patients needed to treat to provide a therapeutic benefit is theoretically infinite, but only 50 patients need to be treated to harm one.

Intervention bias also poses a serious financial threat to the sustainability of health care systems. Since 1970, U.S. health care spending per capita has been more than double the real growth in GDP per capita (4.3 percent vs 2.0 percent) [55]. Over that same period, countries belonging to the Organization for Economic Cooperation and Development (OECD) averaged an annual growth rate of 3.8 percent in health care spending per capita compared to only a 2.1 percent annual growth in GDP per capita. Eight of 20 countries had higher average annual growth rates in health care spending per capita than the United States [55]. A portion of this growth is due to the adoption and over-utilization of technologies that are either futile or confer only minor clinical benefits. Between 1987 and 2000, spending on heart disease increased by greater than 26 billion dollars; 69 percent of which was attributable to increased cost per treated case [56]. During that time, the rate of stenting increased 128 percent [57], despite repeated negative trials involving the use of this modality for its most often cited indication [7-11].

CRITICISMS

One major criticism against the existence of intervention bias in medicine is, if intervention bias exists then why is there undertreatment of major conditions such as hypertension (HTN) and asthma? There are several explanations for undertreatment that do not delegitimize the existence of intervention bias. To some extent, undertreatment, especially as it applies to goal-directed management of chronic illnesses, is actually

a manifestation of intervention bias. Gu et al. reported on trends in anti-hypertension use and blood pressure control in the United States from 2001 to 2010 using NHANES data [58]. Control was identified as $< 140/90$ mmHg for the general population and $< 130/80$ mmHg for patients with diabetes or chronic kidney disease. However, there is no precedent from clinical trials that patients benefit from these targets and they could be harmful. Even the authors' definition of hypertension that justifies treatment, $SBP \geq 140$ and $DBP \geq 90$ mmHg, is not evidence based. A Cochrane meta-analysis found that the pharmacologic treatment of mild hypertension ($SBP < 160$ and $DBP < 100$ mmHg) in patients without major co-morbidities did not reduce the risk of death or non-fatal cardiovascular events compared to placebo [59]. Therefore, it could be said that many cases of undertreatment actually represent evidence-based medicine, and the definitions used by Gu et al. and other investigators are not valid determinants of undertreatment. This issue repeatedly plagues studies looking at compliance and appropriate use. Kerr et al. conducted a retrospective cohort study of diabetic patients within the VA system to determine if appropriate action measures for HTN were met [60]. They found that 94 percent were appropriately treated despite the limitations of goal-directed targets that have been discussed. Interestingly, 8 percent of patients had potential overtreatment, meaning that antihypertensive medications were added or intensified when BP was $< 130/65$ mmHg. Even if one were to grant the definition of undertreatment as valid, factors other than physician treatment recommendations would likely play a more important role such as the limitations of data sources used to assess compliance [61], patient insurance status [58], and patient compliance with physician recommendations.

CONCLUSION

In conclusion, intervention bias is a problem in modern medicine. It corrupts the informed decision-making process and leads physicians to adopt futile and potentially

harmful interventions and continue using them after their benefits have been disproven. Futile interventions subject patients to unnecessary physical harm and thus violate the principle of “*primum non nocere*.” From an economic perspective, the adoption and widespread use of such interventions confers a personal and social welfare loss. Recognition is the first step toward overcoming bias, and physicians must appreciate the limitations that intervention bias poses to the practice of medicine. To guard against it, we should always remain skeptical, insist on rigorous experimentation and reporting of trials that involve hard endpoints, and be unafraid to protest the widespread utilization of interventions that do not pass this test.

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